CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-739

CORRESPONDENCE

noted pls 10/16/98

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

October 13, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/A 1

MINOR AMENDMENT
Amidarone Hydrochloride Tablets 200 mg
ANDA # 74-739

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application No. 74-739 for Amiodarone Hydrochloride Tablets 200 mg.

Further reference is made to our amendment of April 7, 1998 and to the Agency's deficiency letter of September 29, 1998 (attached).

The purpose of this submission is to respond to the Agency's deficiency letter of September 29, 1998. For the convenience of the reviewer, we have reiterated FDA comments followed by our response. In addition, we are providing copies of final printed insert labeling which reflect FDA's request changes.

Should you have any questions regarding this supplemental application, please contact the undersigned at (781) 575-7695.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.
Enclosures:
Archive Copy (blue folder): 1 copy
Chemistry, Manufacturing, Controls Copy (red folder): 1 copy

1998

10/16/98

Page(s) 1

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9/29/98

Chemistry Comments

#38

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

FPL

NDA ORIG AMENDMENT

N/Ac

April 7, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 1507500 Standish Place
Rockville, MD 20855-2773

MAJOR AMENDMENT
Response to Deficiency Letter of March 6, 1998
Amiodarone Hydrochloride Tablets, 200 mg
ANDA # 74-739

Dear Mr. Sporn:

Reference is made to the above Abbreviated New Drug Application submitted August 31, 1995, to the amendment submitted August 22, 1997, and to the Agency's Major Deficiency letter dated March 6, 1998 (copy attached).

Enclosed are full responses (responses 1-5) and supporting documents to the chemistry, manufacturing and controls (CMC), and labeling comments listed in the March 6, 1998 letter.

As part of our response to the deficiency letter, we have provided a copy of the revised proposed master production record in Attachment 1. In addition, we have provided three copies of the new methods validation packages in Attachment 2, as requested by the Agency.

Dissolution data for review by the Division of Bioequivalence in accordance with the Agency's request is provided in Response 5*(i)* on page 6-13 of this submission.

We make reference to a March 11, 1998 telephone conversation with Ms. Cassandra Sherrod, CSO at FDA's Office of Generic Drugs relative to our proposed final printed labeling for the product. Ms. Sherrod informed us that the labeling comments included with the March 6, 1998 deficiency letter are duplicate from the last deficiency letter. Ms. Sherrod further indicated that the labeling is satisfactory and that we should disregard the labeling comments when replying to the March 6, 1998 letter.

However, we have included twelve copies of final printed container labels and insert labeling, as well as the annotated side-by-side comparison with the final printed labeling of the previous version to reflect the replacement of the statement, "Caution: Federal Law Prohibits Dispensing Without Prescription" with "R*x* only" on all of our labeling in accordance with FDA's Modernization Act of 1997.

Since this amendment pertains to the responses in the CMC and labeling areas, it is organized in the following manner for ease of review:

CMC:
Responses 1-5: Responses to CMC questions 1-5

Attachment 1:
Revised proposed master production record for Amiodarone Tablets, 200 mg

Attachment 2:
Three copies of the new methods validation package containing the finished product test procedure, validation reports for the assay, related substances and dissolution test procedures

Labeling:

1. Final printed container labels
2. Final printed insert labeling
3. Side-by-side comparison

Should you have any question regarding the submitted material, please contact the undersigned at (781) 575-7695 or Mr. Gary Lewis at (781) 575-7363.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.

Enclosures:
Archive Copy (blue folder): 1 copy
Chemistry, Manufacturing, Controls Copy (red folder): 1 copy

Page(s) 2

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3/6/98
Chemistry Comments
#38

Labels + labeling satisfactory for approval - labeling review drafted 11/21/97 a Vogt

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

8/22/97

FPL

NDA ORIG AMENDMENT

N/AC

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Amiodarone HCl Tablets 200mg
ANDA# 74-739
MAJOR Amendment (Response to deficiency letter of 6/12/97)

Dear Mr. Sporn:

Reference is made to our ANDA# 74-739 dated 8/95, our Major amendment dated 12/3/96, and to the Agency letters dated 5/96 and 6/12/97. This response has been developed with consideration to the Agency's letters and on the basis of a discussion with Mr. Tim Ames on 7/8/97.

Copley has indeed conducted significant developmental and scale-up experiments from which we derive a high level of confidence on our process and its ability to consistently produce a product that meets specifications. Based on our scale-up experience we have defined our manufacturing process as requested and have provided specific responses that we trust will adequately address the reviewers comments. We are providing a revised proposed master production record that incorporates all the best available input.

We look forward to an expeditious review of this amendment.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

RECEIVED

AUG 25 1997

GENERIC DRUGS

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

8/22/97

Mr. Richard Penta
New England District
Food and Drug Administration
1 Montvale Ave
Stoneham MA 02180-3500

Amiodarone HCl Tablets 200mg
ANDA# 74-739
MAJOR Amendment (Response to deficiency letter of 6/12/97)

Dear Mr. Penta:

Pursuant to 21CFR314.70(b), Copley is forwarding a true copy of a Major amendment to our amiodarone ANDA# 74-739. Copley certifies that the material contained in this "field copy" is a true copy of the same material that was submitted to FDA headquarters.

If there are any questions or concerns regarding these data, please feel free to call or fax at the following numbers: 617-575-7520 (direct dial) or 617-575-7362 (fax).

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

Page(s) 3

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6/12/97
Chemistry Comments
#38

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

December 3, 1996

NDA ORIG AMENDMENT
N/A - Draft

Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

MAJOR AMENDMENT
Amiodarone HCl Tablets, 200 mg
ANDA 74-739

Dear Sir:

Reference is made to our above Abbreviated New Drug Application and to your deficiency letter of May 1996 (attached) which was designated as a MAJOR amendment response. Your deficiency comments followed by our responses are appended to this letter and sorted by question number.

In addition to these responses, we would also like to make you aware of the following correction regarding Corn Starch In order to distinguish between the different grades of in-house Corn Starch Copley has assigned a new internal raw material part number to the rade of Corn Starch ısed in the manufacture of Amiodarone Tablets.

OLD RM No.	NEW RM No.

With the exception of the RM number, all data presented in the original ANDA filing is still applicable. We have provided revised specifications, test methods and a certificate of analysis which now reflect this new RM number. This information is provided at the back of this amendment in ATTACHMENT 1.

We believe that we have adequately addressed all of the issues raised by the Agency and look forward to an expeditious review and approval of this ANDA.

Regards,

Robert Kelly
Manager, Regulatory Affairs

enclosures

RECEIVED
DEC 0 4 1996

ANDA 74-739

Copley Pharmaceutical Inc.
Attention: W.E. Brochue, Ph.D.
Canton Commerce Center
25 John Road
Canton MA 02021

SEP 25 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Amiodarone Hydrochloride Tablets, 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of sodium acetate buffer at pH 5.0 containing using USP 23 Apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

/ Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NAI
Bio reviewer assigned
31 MAY96.
6/12/96

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

NEW CORRESP BIOAVAILABILITY
NC/BIO

May 24, 1996

Mr. Doug Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Bioequivalence Amendment
Amiodarone Hydrochloride Tablets, 200 mg
ANDA 74-739

Dear Sir:

Reference is made to our above Abbreviated New Drug Application which was submitted to the Agency on August 31, 1995. Reference is also made to Dr. Keith Chan's letter dated February 29, 1996, commenting on the dissolution method for the finished product tablets and requesting long-term stability data (-22°C) for desethylamiodarone (copy attached). In response to Dr. Chan's comments we are providing the following:

Comment 1:

The comparative dissolution testing for the products should be conducted following the FDA method which was provided to you by telephone on February 1, 1996 as follows:

Medium:	900 mL sodium acetate buffer at pH 5.0 containing 1% SLS
Apparatus 2:	75 rpm
Units:	12 units each product
Sampling times:	15,30,45, 60 minutes
Tolerance:	0 minutes

Response:

We have conducted comparative dissolution testing on Copley's Amiodarone HCl Tablets, 200 mg (bio lot 133Z01) and the reference product Cordarone (lot 9940936) using the conditions specified above. It is important to point out that the Agency did not specify the sodium acetate buffer strength to be used. Since there are two buffer strengths described in the USP (0.05M and 0.022M, pH 5), both were evaluated and reported. ATTACHMENT 1 contains comparative dissolution profiles using both strengths of sodium acetate buffer generated under the above dissolution conditions. It is our intent to use the 0.05M sodium acetate buffer strength in our dissolution method. For reference purposes, we have also generated dissolution profiles on our stability

samples stored under CRT and accelerated conditions using the conditions (0.05M sodium acetate buffer) specified above. These stability dissolution profiles can also be found in ATTACHMENT 1.

To comply with this dissolution method, we have also revised and re-validated our dissolution test method. Copies of our revised test method (QC83-133) and validation report (QC83(VAL)-133) are provided in ATTACHMENT 2.

Comment 2:

Submit the stability data for desethylamiodarone under long-term storage at -22° C.

Response:

On September 12, 1995, amended their report entitled "Validation of a ohic Method Using Detection for the Determination of Amiodarone and Desethylamiodarone in Human Plasma" by providing the results of standard curve and quality control sample data, as well as recovery and stability data. During this validation, long term stability evaluation was performed three times with deviations outside of the acceptable range at each retest. However, analysis of the test curve indicated that the deviation was most likely due to spiking factors and not sample instability. A subsequent revalidation which was undertaken by in April 1996, showed that Amiodarone and desethylamiodarone were stable at a nominal temperature of -22° C for 136 days.

In addition, the limits of quantitation for desethylamiodarone and amiodarone in the September 1995 report were mistakenly reported as 4.98 and 4.97 ng/ml, respectively when they should be 5.03 and 5.01 ng/ml, respectively. ATTACHMENT 3 contains copies of both the September 1995 and April 1996 validation reports.

We believe that the information provided within this amendment adequately addresses your comments and request for data. We look forward to your expeditious review and approval of this application

Sincerely,

Robert Kelly
Manager, Product Registrations
Copley Pharmaceutical, Inc.
(617) 575-7363

ATTACHMENTS

Desk copy: Dr. Keith Chan
Director, Division of Bioequivalence

ANDA 74-739

Copley Pharmaceutical Inc.
Attention: W. E. Brochu, Ph.D.
Canton Commerce Center
25 John Road
Canton, MA 02021-2897

Dear Dr. Brochu:

This is in reference to your abbreviated new drug application dated August 31, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Amiodarone Hydrochloride Tablets, 200 mg.

Reference is also made to your amendment dated October 26, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

Page(s) 1

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5/96

20. Please include limits for individual degradants in the stability report.

21. What is the reason for 100's at 1 month accelerated station meeting dissolution specification at S2 level?

22. Please submit any available CRT stability data

B. Labeling Deficiencies

1. CONTAINER 60s, 100s, 250s

a. Please assure that the established name and strength appear prominently on the labels.

b. Revise the established name to read:

Amiodarone Hydrochloride Tablets

c. Revise the storage recommendations to read:

Store at Controlled Room Temperature
20-25°C (68-77°F) [see USP]

d. Dispense in a tight, light-resistant container.

2. INSERT

a. GENERAL COMMENT

Minor revisions, which are mostly editorial, are indicated on the enclosed mock-up of your draft labeling.

b. DESCRIPTION

Revise the second sentence to read:

In addition, each tablet also contains the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, povidone, corn starch and ...

c. PRECAUTIONS

i. Surgery - Replace the last sentence in this subsection "One possible" with the following:

Until further studies have been performed, it is recommended that FiO_2 and the determinants of oxygen delivery to the tissues (e.g., SaO_2, PaO_2) be closely monitored in patients on amiodarone.

ii. Pediatric Use

...in pediatric patients have...

d. HOW SUPPLIED

i. Revise to read:

Amiodarone HCl tablets are available in bottles of: (delete the word "tablets").

ii. Include the tablet's color (pink) in this section.

iii. Revise the storage recommendations to read:

Store at Controlled Room Temperature 20-25°C (68-77°F) [see USP]

Please revise your labels and labeling, as instructed above, and submit draft container labels and insert labeling.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. The dissolution test, method and specifications have been reviewed by our Division Of Bioequivalence. Their conclusions were communicated to you in a letter, dated February 29, 1996.

2. We have submitted your test methods for validation by our district laboratories. Please provide samples when requested by the field personnel.

3. We have requested an inspection of your manufacturing facilities by our field personnel. Please note that the manufacturing facility must be found to operate in compliance with cGMPs before this application may be approved.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial

disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 5/14/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Labeling

1.1 Holcombe, F.

-739

FEB 29 1996

Copley Pharmaceutical Inc.
Attention: W. E. Brochu, Ph.D.
Canton Commerce Center
25 John Road
Canton, MA 02021

Dear Dr. Brochu:

Reference is made to the Abbreviated New Drug Application, submitted on August 31, 1995 for Amiodarone Hydrochloride Tablets, 200 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The comparative dissolution testing for the products should be conducted following the FDA method which was provided to you by telephone on February 1, 1996 as follows:

Medium:	900 mL sodium acetate buffer at pH 5.0 containing 1% SLS
Apparatus 2:	75 rpm
Units:	12 units each product
Sampling times:	15,30,45, 60 minutes
Tolerance:	es

2. Submit the stability data for desethylamiodarone under long-term storage at -22°C.

NOTE: In future submission, review will be considerably easier if assayed potency and content uniformity data for both the test and reference products are submitted with the *in vitro* dissolution data.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-739

Copley Pharmaceutical Inc.
Attention: William E. Brochu
Canton Commerce Center
25 John Road
Canton, MA 02021

OCT 30 1995

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Amiodarone Hydrochloride Tablets, 200 mg

DATE OF APPLICATION: August 31, 1995

DATE OF RECEIPT: September 5, 1995

We will correspond with you further after we have had the opportunity to review of your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Tim Ames
Consumer Safety Officer
(301) 594-0360

Sincerely yours,

/S/

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Ack
Harvey Meadow
9/22/95
9/25/95

Copley Pharmaceutical Inc.
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Fax:
Canton (617) 821-4068
Boston (617) 268-4394
N.J. (201) 894-1553

Charles Ganley, M.D.
Acting Director,
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville MD 20855-2773

Pulmonary review done 3/19/96 aVS
Amiodarone Cordarone a/p 10/18/95

Date AUG 31 1995

RE: ANDA Submission
Amiodarone HCl Tablets 200mg

Dear Dr. Ganley:

Copley Pharmaceutical Inc. respectfully submits for your Division's review our Abbreviated New Drug application for Amiodarone HCl Tablets 200mg strength.

This application is submitted in accordance with the guidelines set forth in Section 505(j) of the Federal, Food, Drug, and Cosmetic Act. This application contains a bioequivalance study report that was designed and conducted with consideration to applicable Agency guidelines and expectations. The data demonstrate our product to be equivalent to the branded product and therefore we request an AB rating in FDA's listing of Approved Drug Products with Therapeutic Equivalence Evaluations. The bioequivalence trial was conducted by , located in The copy intended for the Pharmacokinetics reviewer (orange jacket) contains a 3.5" flopydisk with the raw data for the bioequivalence trial along with a print out from that disk.

A separate copy of this submission is being sent to the Boston District Office of the FDA, in compliance with the Federal Register Notice of September 1993.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

Enclosures: Archive Copy (blue jacket),
Manufacturing Section (red jacket)
Bioequivalence Study Report (orange jacket)
2 copies of the Analytical Section (XVI) in separate binder